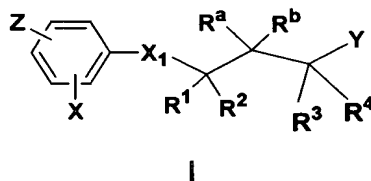


CLAIMS

We claim:

- 5 1. A compound of the formula



- 10 wherein  $X_1$  is O,  $S(O)_n$ ,  $-\overset{\overset{R^5}{|}}{N}-$ ,  $co-\overset{\overset{R^5}{|}}{N}-$ , or  $-CH_2-$ , with the proviso that when  $X_1$  is  $-CH_2-$ ,  $R_1$  and  $R_2$  are only halogen.

$n$  is 0, 1 or 2;

- 15  $R^a$  and  $R^b$  when taken together form an oxo ( $=O$ ) group, or  $R^a$  and  $R^b$  are each independently hydrogen, OH,  $OCOR^9$ ,  $NH_2$ ,  $N_3$ ,  $NHCOOR^9$ ,  $NHCOCOR^9$ ,  $NHSO_2R^9$  or F;

- 20  $X$  is H,  $CF_3$ ,  $OCF_3$ , halogen,  $C_1-C_7$  alkyl,  $C_2-C_7$  alkenyl,  $C_2-C_7$  alkynyl or  $C_3-C_7$  cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by  $COOR^8$ ,  $CN$ ,  $C(O)NR^6R^7$ ,  $PO_3R^8$ ,  $SO_3R^8$ , heterocyclic,  $OR^8$ ,  $SH$ ,  $S(O)_nR^9$ ,  $NR^6R^7$ ,  $NH(CO)NR^6R^7$ ,  $NH(CO)OR^9$ , aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from  $NR^6R^7$ ,  $OR^8$ ,  $COOR^8$ ,  $SO_3R^8$ ,  $OCOR^9$ ,  $PO_3R^8$ ,  $C(O)NR^6R^7$  or heterocyclic;

25

$R_1$  and  $R_2$  are each independently H, halogen,  $OR^9$ ,  $C_1-C_7$  alkyl,  $C_2-C_7$  alkynyl,  $C_2-C_7$  alkynyl or  $C_3-C_7$  cycloalkyl, said alkyl, alkenyl, alkynyl or

cycloalkyl group being optionally substituted by COOR<sup>8</sup>, CN, C(O)NR<sup>6</sup>R<sup>7</sup>, PO<sub>3</sub>R<sup>8</sup>, SO<sub>3</sub>R<sup>8</sup>, heterocyclic, OR<sup>8</sup>, SH, S(O)<sub>n</sub>R<sup>9</sup>, NR<sup>6</sup>R<sup>7</sup>, NH(CO)NR<sup>6</sup>R<sup>7</sup>, NH(CO)OR<sup>9</sup>, OC(O)OR<sup>9</sup>, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted with one or two groups independently selected from

5 NR<sup>6</sup>R<sup>7</sup>, OR<sup>8</sup>, COOR<sup>8</sup>, SO<sub>3</sub>R<sup>8</sup>, OCOR<sup>9</sup>, PO<sub>3</sub>R<sup>8</sup>, C(O)NR<sup>6</sup>R<sup>7</sup> or heterocyclic;

R<sup>3</sup>, R<sup>4</sup> and Y are each independently H, halogen, OR<sup>10</sup>, S(O)<sub>n</sub>R<sup>10</sup>, C<sub>1</sub>–C<sub>7</sub> alkyl, C<sub>2</sub>–C<sub>7</sub> alkenyl, C<sub>2</sub>–C<sub>7</sub> alkynyl or C<sub>3</sub>–C<sub>7</sub> cycloalkyl, said alkyl,

10 alkenyl, alkynyl or cycloalkyl group being optionally substituted by COOR<sup>8</sup>, CN, C(O)NR<sup>6</sup>R<sup>7</sup>, PO<sub>3</sub>R<sup>8</sup>, SO<sub>3</sub>R<sup>8</sup>, heterocyclic, OR<sup>8</sup>, SH, S(O)<sub>n</sub>R<sup>9</sup>, NR<sup>6</sup>R<sup>7</sup>, NH(CO)NR<sup>6</sup>R<sup>7</sup>, NH(CO)OR<sup>9</sup>, OC(O)OR<sup>9</sup>, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from NR<sup>6</sup>R<sup>7</sup>, OR<sup>8</sup>, COOR<sup>8</sup>, SO<sub>3</sub>R<sup>8</sup>,

15 OCOR<sup>9</sup>, PO<sub>3</sub>R<sup>8</sup>, C(O)NR<sup>6</sup>R<sup>7</sup> or heterocyclic, with the proviso that not all of R<sup>3</sup>, R<sup>4</sup> and Y may be the same halogen;

R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> are each independently H, C<sub>1</sub>–C<sub>7</sub> alkyl, C<sub>2</sub>–C<sub>7</sub> alkenyl, C<sub>2</sub>–C<sub>7</sub> alkynyl or C<sub>3</sub>–C<sub>7</sub> cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl

20 group being optionally substituted by COOR<sup>8</sup>, CN, OR<sup>8</sup>, NR<sup>8</sup>R<sup>9</sup>, SO<sub>3</sub>R<sup>8</sup>, PO<sub>3</sub>R<sup>8</sup>, halogen, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from COOR<sup>8</sup>, SO<sub>3</sub>R<sup>8</sup>, PO<sub>3</sub>R<sup>8</sup> or heterocyclic;

25 R<sup>8</sup> is H, C<sub>1</sub>–C<sub>7</sub> saturated straight chain alkyl or cycloalkyl;

R<sup>9</sup> is same as R<sup>8</sup> but is not hydrogen;

- R<sup>10</sup> is C<sub>1</sub>–C<sub>7</sub> alkyl, C<sub>2</sub>–C<sub>7</sub> alkenyl, C<sub>2</sub>–C<sub>7</sub> alkynyl or C<sub>3</sub>–C<sub>7</sub> cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by COOR<sup>8</sup>, CN, C(O)NR<sup>6</sup>R<sup>7</sup>, PO<sub>3</sub>R<sup>8</sup>, SO<sub>3</sub>R<sup>8</sup>, heterocyclic, OR<sup>8</sup>, SH, S(O)<sub>n</sub>R<sup>9</sup>, NR<sup>6</sup>R<sup>7</sup>, NH(CO)NR<sup>6</sup>R<sup>7</sup>, NH(CO)OR<sup>9</sup>, aryl or heteroaryl, said
- 5 aryl or heteroaryl being optionally substituted by one or two groups independently selected from NR<sup>6</sup>R<sup>7</sup>, OR<sup>8</sup>, COOR<sup>8</sup>, SO<sub>3</sub>R<sup>8</sup>, OCOR<sup>8</sup>, PO<sub>3</sub>R<sup>8</sup>, C(O)NR<sup>6</sup>R<sup>7</sup> or heterocyclic;

Z is OR<sup>11</sup>, S(O)<sub>n</sub>R<sup>11</sup>, NR<sup>11</sup>R<sup>12</sup> or CHR<sup>11</sup>R<sup>12</sup>;

10

R<sup>11</sup> and R<sup>12</sup> are each independently hydrogen, C<sub>1</sub>–C<sub>7</sub> alkyl, C<sub>2</sub>–C<sub>7</sub> alkenyl, C<sub>2</sub>–C<sub>7</sub> alkynyl or C<sub>3</sub>–C<sub>7</sub> cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by NR<sup>13</sup>R<sup>14</sup>, S(O)<sub>n</sub>R<sup>13</sup>, OR<sup>13</sup>, with the proviso that both R<sup>11</sup> and R<sup>12</sup> may not be hydrogen;

15

R<sup>13</sup> and R<sup>14</sup> are each independently H, SiR<sup>15</sup>R<sup>16</sup>R<sup>17</sup>, C<sub>1</sub>–C<sub>7</sub> alkyl, C<sub>2</sub>–C<sub>7</sub> alkenyl, C<sub>2</sub>–C<sub>7</sub> alkynyl, aryl or C<sub>3</sub>–C<sub>7</sub> cycloalkyl, said alkyl, alkenyl, alkynyl, aryl or cycloalkyl group being optionally substituted by one to three groups independently selected from COOR<sup>8</sup>, OR<sup>8</sup>, Si R<sup>15</sup>R<sup>16</sup>R<sup>17</sup>,

20

OR<sup>15</sup>, aryl, biaryl or heteroaryl, said aryl, biaryl or heteroaryl being optionally substituted with one to three groups independently selected from halogen, CF<sub>3</sub>, OR<sup>8</sup>, COOR<sup>8</sup>, NO<sub>2</sub>, or CN;

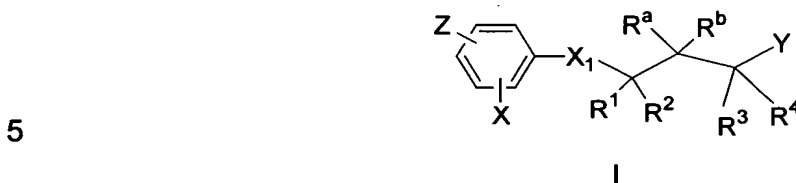
- R<sup>13</sup> and R<sup>14</sup> when taken together may form a 5 –7 membered
- 25 heterocyclic ring with one or more heteroatoms selected from O, N and S; said ring being optionally substituted by OR<sup>8</sup>, COOR<sup>8</sup>, or C(O)NR<sup>5</sup>R<sup>6</sup>;

R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> are each independently aryl, benzyl, benzhydryl, biaryl, heteroaryl, (C<sub>1</sub>–C<sub>6</sub>) alkyl–aryl or (C<sub>1</sub>–C<sub>6</sub>) alkyl–heteroaryl, said aryl radical



being optionally substituted by halogen,  $\text{CF}_3$ ,  $\text{OR}^8$ ,  $\text{COOR}^8$ ,  $\text{NO}_2$ ,  $\text{CN}$ ,  $\text{C}_1\text{-C}_7$  alkyl.

2. A compound of the formula



or a pharmaceutically acceptable salt thereof wherein

10  $X_1$  is O,  $\text{S(O)}_n$ ,  $\text{—}\overset{\text{R}^5}{\text{N}}\text{—}$ ,  $\text{co—}\overset{\text{R}^5}{\text{N}}\text{—}$  or  $\text{—CH}_2\text{—}$ , with the proviso that when  $X_1$  is  $\text{—CH}_2\text{—}$ ,  $\text{R}_1$  and  $\text{R}_2$  are only halogen.

$n$  is 0, 1 or 2;

15  $\text{R}^a$  and  $\text{R}^b$  when taken together form an oxo ( $=\text{O}$ ) group, or  $\text{R}^a$  and  $\text{R}^b$  are each independently hydrogen, OH,  $\text{OCOR}^9$ ,  $\text{NH}_2$ ,  $\text{N}_3$ ,  $\text{NHCOOR}^9$ ,  $\text{NHCOCOR}^9$ ,  $\text{NHSO}_2\text{R}^9$  or F.

20  $X$  is H,  $\text{CF}_3$ ,  $\text{OCF}_3$ , halogen,  $\text{C}_1\text{—C}_7$  alkyl,  $\text{C}_2\text{—C}_7$  alkenyl,  $\text{C}_2\text{—C}_7$  alkynyl or  $\text{C}_3\text{—C}_7$  cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by  $\text{COOR}^8$ ,  $\text{CN}$ ,  $\text{C(O)NR}^6\text{R}^7$ ,  $\text{PO}_3\text{R}^8$ ,  $\text{SO}_3\text{R}^8$ , heterocyclic,  $\text{OR}^8$ , SH,  $\text{S(O)}_n\text{R}^9$ ,  $\text{NR}^6\text{R}^7$ ,  $\text{NH(CO)NR}^6\text{R}^7$ ,  $\text{NH(CO)OR}^9$ , aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from  $\text{NR}^6\text{R}^7$ ,  $\text{OR}^8$ ,  $\text{COOR}^8$ ,  $\text{SO}_3\text{R}^8$ ,  $\text{OCOR}^9$ ,  $\text{PO}_3\text{R}^8$ ,  $\text{C(O)NR}^6\text{R}^7$  or heterocyclic;



- $R^1$  and  $R^2$  are each independently H, halogen,  $OR^9$ ,  $C_1-C_7$  alkyl,  $C_2-C_7$  alkenyl,  $C_2-C_7$  alkenyl or  $C_3-C_7$  cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by  $COOR^8$ , CN,  $C(O)NR^6R^7$ ,  $PO_3R^8$ ,  $SO_3R^8$ , heterocyclic,  $OR^8$ , SH,  $S(O)_nR^9$ ,  $NR^6R^7$ ,  $NH(CO)NR^6R^7$ ,  $NH(CO)OR^9$ ,  $OC(O)OR^9$ , aryl or heteroaryl, said aryl or heteroaryl being optionally substituted with one or two groups independently selected from  $NR^6R^7$ ,  $OR^8$ ,  $COOR^8$ ,  $SO_3R^8$ ,  $OCOR^9$ ,  $PO_3R^8$ ,  $C(O)NR^6R^7$  or heterocyclic;
- 5
- 10  $R^3$ ,  $R^4$  and Y are each independently H,  $OR^{10}$ ,  $S(O)_nR^{10}$ ,  $C_1-C_7$  alkyl,  $C_2-C_7$  alkenyl,  $C_2-C_7$  alkynyl or  $C_3-C_7$  cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by  $COOR^8$ , CN,  $C(O)NR^6R^7$ ,  $PO_3R^8$ ,  $SO_3R^8$ , heterocyclic,  $OR^8$ , SH,  $S(O)_nR^9$ ,  $NR^6R^7$ ,  $NH(CO)NR^6R^7$ ,  $NH(CO)OR^9$ ,  $OC(O)OR^9$ , aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from  $NR^6R^7$ ,  $OR^8$ ,  $COOR^8$ ,  $SO_3R^8$ ,  $OCOR^8$ ,  $PO_3R^8$ ,  $C(O)NR^6R^7$  or heterocyclic;
- 15
- 20  $R^5$ ,  $R^6$  and  $R^7$  are each independently H,  $C_1-C_7$  alkyl,  $C_2-C_7$  alkenyl,  $C_2-C_7$  alkynyl or  $C_3-C_7$  cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by  $COOR^8$ , CN,  $OR^8$ ,  $NR^8R^9$ ,  $SO_3R^8$ ,  $PO_3R^8$ , halogen, aryl or heteroaryl, said aryl or heteroaryl being optionally substituted by one or two groups independently selected from  $COOR^8$ ,  $SO_3R^8$ ,  $PO_3R^8$  or heterocyclic;
- 25
- $R^8$  is H,  $C_1-C_7$  saturated straight chain alkyl or cycloalkyl,  $CF_3$  or  $CH_2CF_3$ ;
- $R^9$  is same as  $R^8$  but is not hydrogen;

- R<sup>10</sup> is C<sub>1</sub>–C<sub>7</sub> alkyl, C<sub>2</sub>–C<sub>7</sub> alkenyl, C<sub>2</sub>–C<sub>7</sub> alkynyl or C<sub>3</sub>–C<sub>7</sub> cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by COOR<sup>8</sup>, CN, C(O)NR<sup>6</sup>R<sup>7</sup>, PO<sub>3</sub>R<sup>8</sup>, SO<sub>3</sub>R<sup>8</sup>, heterocyclic, OR<sup>8</sup>, SH, S(O)<sub>n</sub>R<sup>9</sup>, NR<sup>6</sup>R<sup>7</sup>, NH(CO)NR<sup>6</sup>R<sup>7</sup>, NH(CO)OR<sup>9</sup>, aryl or heteroaryl, said
- 5 aryl or heteroaryl being optionally substituted by one or two groups independently selected from NR<sup>6</sup>R<sup>7</sup>, OR<sup>8</sup>, COOR<sup>8</sup>, SO<sub>3</sub>R<sup>8</sup>, OCOR<sup>8</sup>, PO<sub>3</sub>R<sup>8</sup>, C(O)NR<sup>6</sup>R<sup>7</sup> or heterocyclic;

- Z is OR<sup>11</sup>, S(O)<sub>n</sub>R<sup>11</sup>, NR<sup>11</sup>R<sup>12</sup> or CHR<sup>11</sup>R<sup>12</sup>;
- 10 R<sup>11</sup> and R<sup>12</sup> are each independently hydrogen, C<sub>1</sub>–C<sub>7</sub> alkyl, C<sub>2</sub>–C<sub>7</sub> alkenyl, C<sub>2</sub>–C<sub>7</sub> alkynyl or C<sub>3</sub>–C<sub>7</sub> cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally substituted by NR<sup>13</sup>R<sup>14</sup>, S(O)<sub>n</sub>R<sup>13</sup>, OR<sup>13</sup>, with the proviso that both R<sup>11</sup> and R<sup>12</sup> may not be hydrogen;
- 15 R<sup>13</sup> and R<sup>14</sup> are each independently H, SiR<sup>15</sup>R<sup>16</sup>R<sup>17</sup>, C<sub>1</sub>–C<sub>7</sub> alkyl, C<sub>2</sub>–C<sub>7</sub> alkenyl, C<sub>2</sub>–C<sub>7</sub> alkynyl, aryl or C<sub>3</sub>–C<sub>7</sub> cycloalkyl, said alkyl, alkenyl, alkynyl, aryl or cycloalkyl group being optionally substituted by one to three groups independently selected from COOR<sup>8</sup>, OR<sup>8</sup>, Si R<sup>15</sup>R<sup>16</sup>R<sup>17</sup>,
- 20 OR<sup>15</sup>, aryl, biaryl or heteroaryl, said aryl, biaryl or heteroaryl being optionally substituted with one to three groups independently selected from halogen, CF<sub>3</sub>, OR<sup>8</sup>, COOR<sup>8</sup>, NO<sub>2</sub>, or CN;

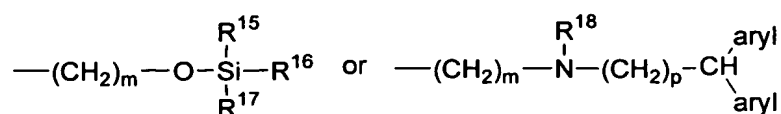
- R<sup>13</sup> and R<sup>14</sup> when taken together may form a 5 – 7 membered
- 25 heterocyclic ring with one or more heteroatoms selected from O, N and S; said ring being optionally substituted by OR<sup>8</sup>, COOR<sup>8</sup>, or C(O)NR<sup>5</sup>R<sup>6</sup>;

R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup> are each independently aryl, benzyl, benzhydryl, biaryl, heteroaryl, (C<sub>1</sub>–C<sub>6</sub>) alkyl–aryl or (C<sub>1</sub>–C<sub>6</sub>) alkyl–heteroaryl, said aryl radical

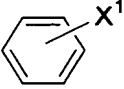
being optionally substituted by halogen,  $\text{CF}_3$ ,  $\text{OR}^8$ ,  $\text{COOR}^8$ ,  $\text{NO}_2$ ,  $\text{CN}$ , or  $\text{C}_1\text{--C}_7$  alkyl.

3. A compound of claim 2 wherein  $\text{X}_1$  is O, or  $\text{S}(\text{O})_n$  and Y is  $\text{OR}^{10}$  in  
 5 which  $\text{R}^{10}$  is  $\text{C}_1\text{--C}_7$  alkyl,  $\text{C}_2\text{--C}_7$  alkenyl,  $\text{C}_2\text{--C}_7$  alkynyl or  $\text{C}_3\text{--C}_7$   
 cycloalkyl, said alkyl, alkenyl, alkynyl or cycloalkyl group being optionally  
 substituted by  $\text{COOR}^8$ ,  $\text{CN}$ ,  $\text{C}(\text{O})\text{NR}^6\text{R}^7$ ,  $\text{PO}_3\text{R}^8$ ,  $\text{SO}_3\text{R}^8$ , heterocyclic,  
 $\text{OR}^8$ ,  $\text{SH}$ ,  $\text{S}(\text{O})_n\text{R}^9$ ,  $\text{NR}^6\text{R}^7$ ,  $\text{NH}(\text{CO})\text{NR}^6\text{R}^7$ ,  $\text{NH}(\text{CO})\text{OR}^9$ , aryl or  
 heteroaryl, said aryl or heteroaryl being optionally substituted by one or  
 10 two groups independently selected from  $\text{NR}^6\text{R}^7$ ,  $\text{OR}^8$ ,  $\text{COOR}^8$ ,  $\text{SO}_3\text{R}^8$ ,  
 $\text{OCOR}^9$ ,  $\text{PO}_3\text{R}^8$ ,  $\text{C}(\text{O})\text{NR}^6\text{R}^7$  or heterocyclic, said  $\text{R}^6$ ,  $\text{R}^7$ ,  $\text{R}^8$  and  $\text{R}^9$   
 substituents being defined as in claim 2.
4. A compound of claim 3 in which  $\text{R}^a$  and  $\text{R}^b$  taken together  
 15 represent an oxo ( $=\text{O}$ ) group, or  $\text{R}^a$  and  $\text{R}^b$  are each independently  
 hydrogen or OH.
5. A compound of claim 3 wherein  $\text{R}^a$  and  $\text{R}^b$  are each independently  
 hydrogen,  $\text{OCOR}^9$ ,  $\text{NH}_2$ ,  $\text{N}_3$ ,  $\text{NHCOOR}^9$  or  $\text{NHCOCOR}^9$  in which  $\text{R}^9$  is as  
 20 defined in claim 2.
6. A compound of claim 4 wherein  $\text{R}^1$  and  $\text{R}^2$  are each independently  
 halogen.
7. A compound of claim 3, 4, 5 or 6 in which

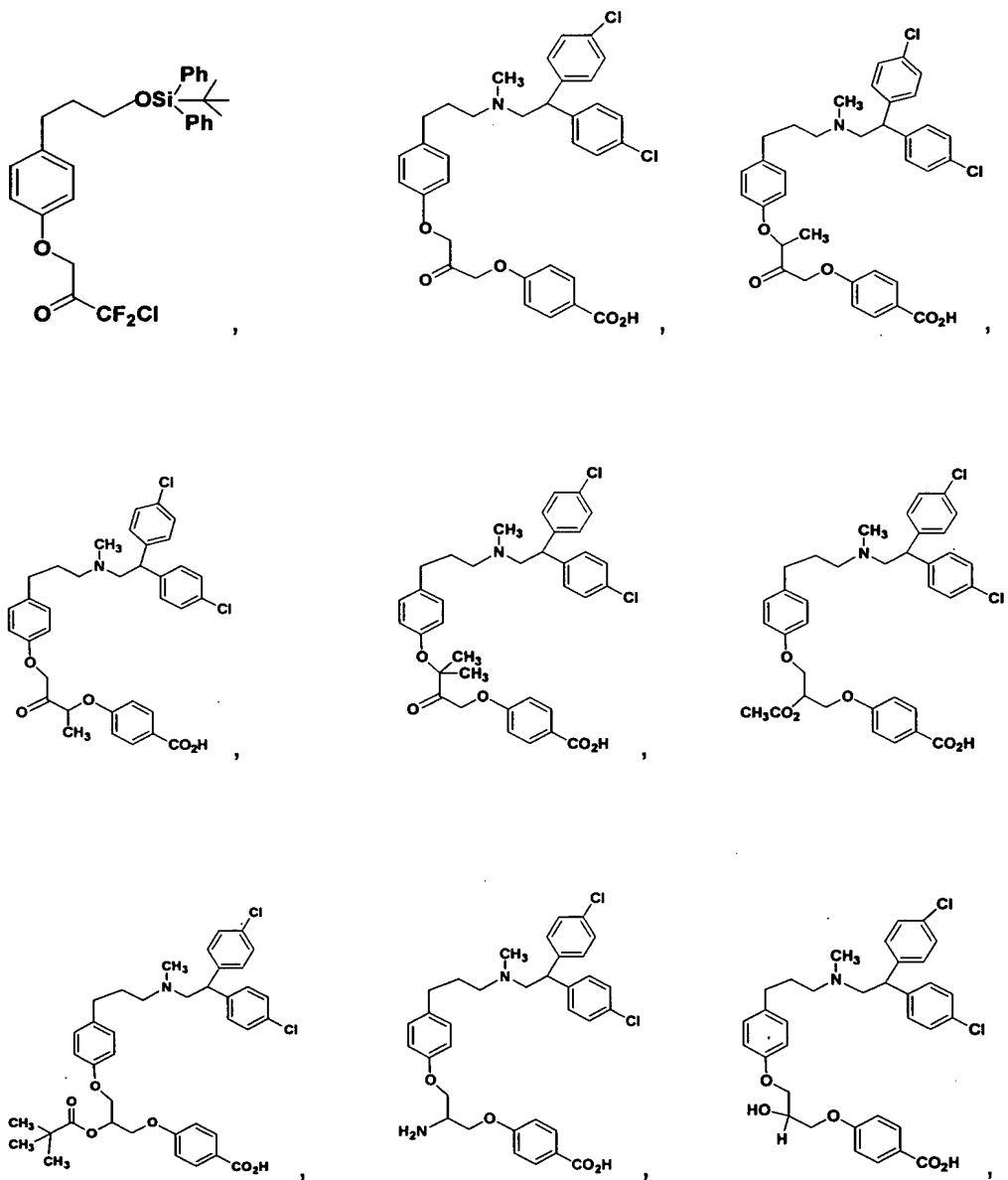
Z is



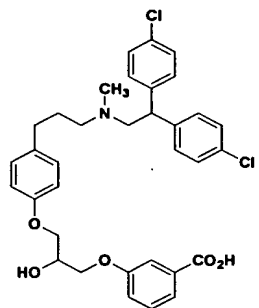
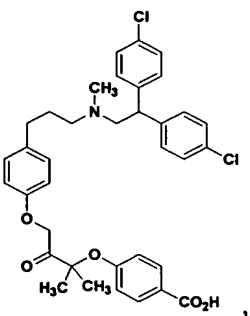
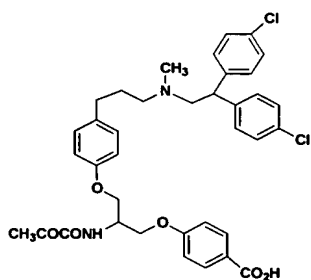
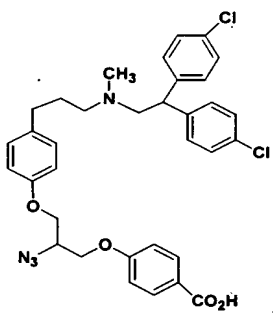
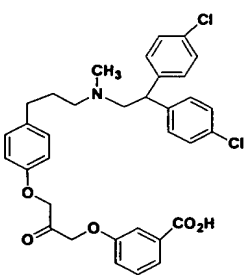
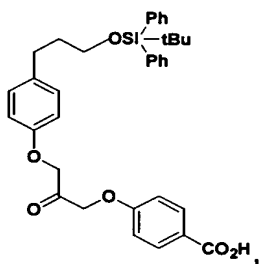
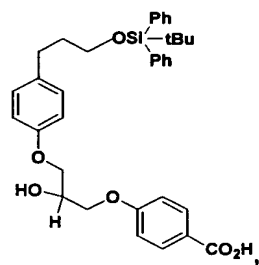
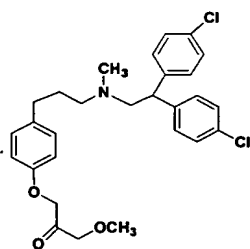
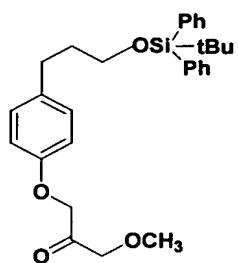
in which m and p each independently represent an integer of one to six,  
 $R^{15}$ ,  $R^{16}$ ,  $R^{17}$  are each independently  $C_1$ – $C_7$  alkyl,  $R^{18}$  is  $C_1$ – $C_7$  alkyl and

aryl represents  in which  $X^1$  is halogen.

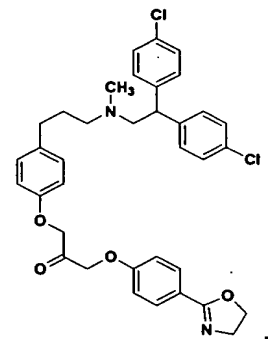
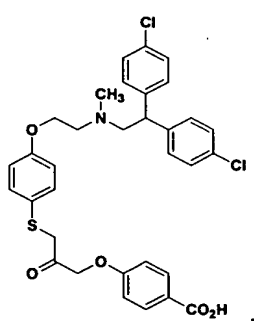
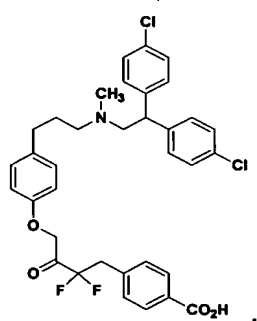
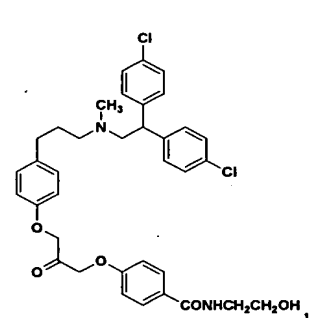
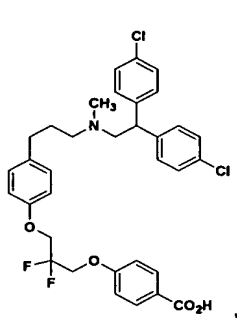
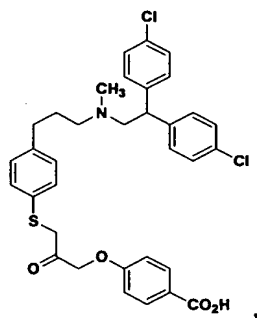
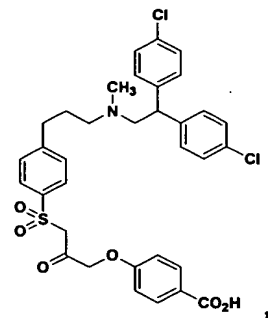
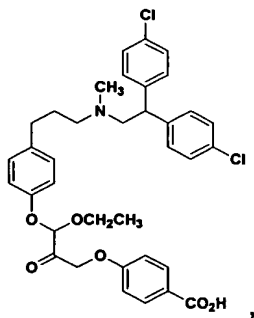
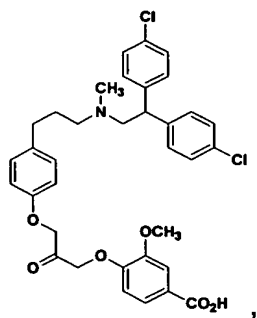
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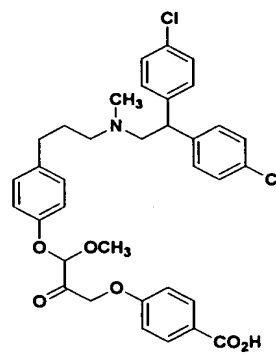
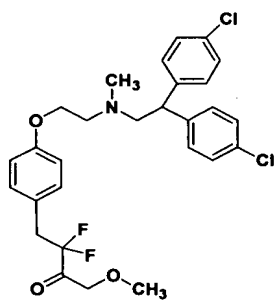
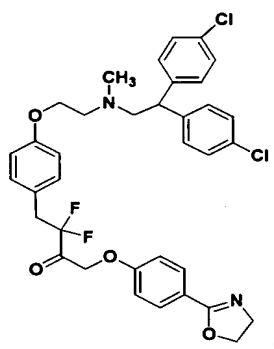
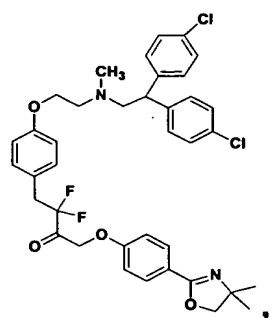
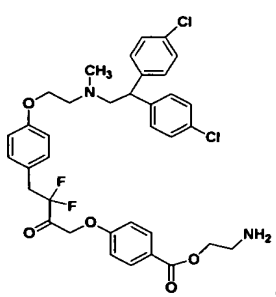
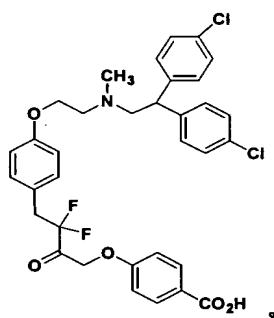
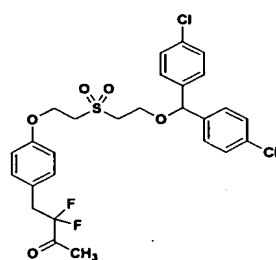
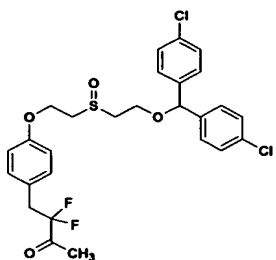
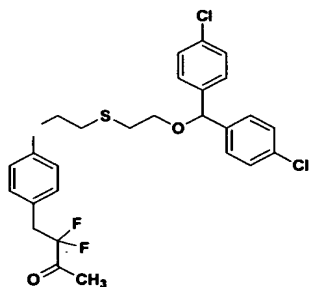




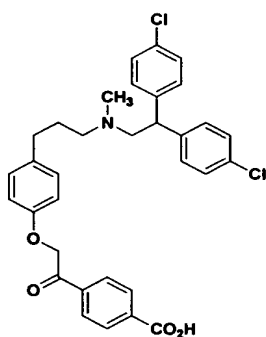
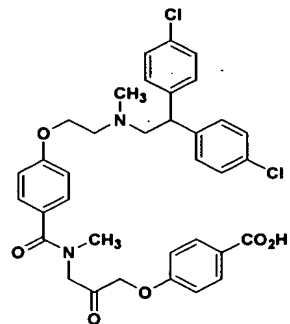
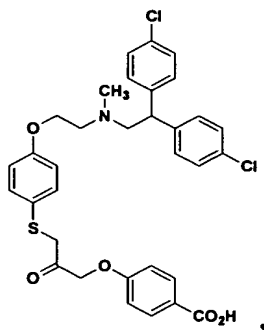
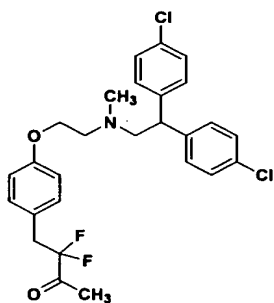


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or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition for the inhibition of cytosolic phospholipase A<sub>2</sub> comprising a therapeutically effective amount of a compound of claim 1 and a pharmaceutically acceptable carrier.
10. A method of inhibiting cytosolic phospholipase A<sub>2</sub> in a mammal in need thereof, comprising administering to said mammal a therapeutically effective amount of a compound of claim 1.